P-21: Biophysics

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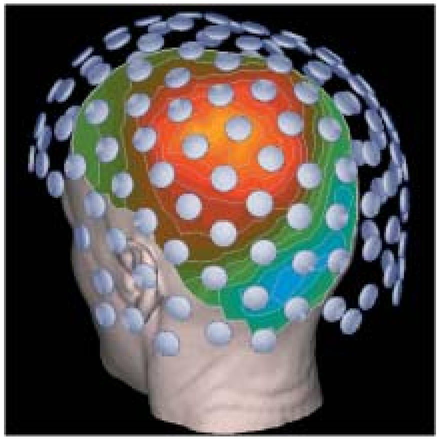


Figure 1. Our whole-head MEG system uses SQUID sensors to record the magnetic fields produced by active populations of neurons.

Introduction

The Biophysics Group (P-21) was founded in 1988 with the goal of applying the scientific and technical resources of Physics Division to the biosciences. Our mission is to contribute to an understanding of biological phenomena by means of the scientific, technical, and conceptual resources of physics; to use biological systems to elucidate general physical principles underlying complex phenomena; and to apply, where appropriate, our scientific and technical capabilities to core Laboratory programs.

Just as the 20th century is regarded as the century of the physical sciences, the 21st century will likely become the century of the biological sciences. P-21 and biophysics as a discipline are well-positioned to contribute to this biological revolution-in-progress through our emphasis on understanding biological systems using the scientific, technical, and conceptual resources of physics. Recent advances in biophysical measurement and in molecular biology are beginning to allow detailed physical understanding of biological phenomena that were previously understood only in qualitative terms.[1] P-21 is well placed by virtue of its capabilities and research interests to contribute significantly to this important trend in the biosciences.

In addition to the goal of achieving a physical understanding of biological phenomena, research in P-21 shares a number of other common characteristics. Specifically,

- we investigate the relationships between structure, dynamics, and function of biological phenomena over a wide range of scales (*e.g.*, from biomolecules to the whole human brain);
- we make extensive use of detection, imaging, and reconstruction techniques (*e.g.*, x-ray crystallography, single-molecule electrophoresis, high-speed photon-counting optical imaging, magnetic resonance imaging [MRI], and magnetic-field measurements using technologies based on superconducting quantum interference devices [SQUIDs] as shown in Figure 1);
- we attempt to achieve a detailed interplay between high-resolution physical measurement and large-scale computational modeling and analysis of complex systems;
- we develop new facilities in support of our scientific and technical goals, including
  - a dedicated x-ray beam line for protein crystallography at the National Synchrotron Light Source at Brookhaven National Laboratory (Brookhaven);
  - a large-bore MRI facility;
  - a high-speed, time-domain measurements and electronics laboratory and fabrication facility; and
  - a growing SQUID applications laboratory at Los Alamos;
- we depend heavily on the tight connection and daily interplay between biologists and physical scientists within the group, the division, and the Laboratory; and
- we apply the knowledge, techniques, and capabilities developed in our biological studies to problems of national security and those of specific interest to the Laboratory when our ongoing efforts can offer unique solutions and significant mutual benefit.

During the past two years, P-21 had a number of major accomplishments, including successful demonstration of both active and passive photon-counting imaging for a variety of applications, significant contributions to measurement and analysis of magnetic fields for functional human brain imaging, and award of a National Institutes of Health (NIH) Center Grant for a LANL-led research initiative in structural genomics. Our scientific and technical activity lies in six major areas, which are discussed individually below.

Protein Structure, Dynamics, and Function

P-21 researchers and collaborators in Bioscience (B) Division and elsewhere have been developing and promoting the field of structural genomics over the last four years. This year, the dream of a broad-based attack on protein structures has been made real through establishment of a NIH-funded Center for Structural Genomics based in Los Alamos. Associated with the Center is an international consortium, the Mycobacterium Tuberculosis Structural Genomics Consortium. This consortium consists of 60 laboratories from 30 institutions in 9 countries. It has the stated goal of solving and analyzing roughly 400 structures of proteins from the bacterium that causes the disease tuberculosis (TB). TB kills more adult humans in the world than any other pathogenic organism. The resulting database of linked structural and functional information is expected to form a lasting basis for understanding pathogenesis by TB bacteria and should pinpoint new targets for drug action against the disease.

To accomplish this, we are developing scalable technologies that will make structural genomics feasible. Further, we will demonstrate an approach to structural genomics that allows researchers around the world to collaborate on a defined set of structural targets. Consortium laboratories have collectively thus far been responsible for 3.3% of all protein structures in the Protein Data Bank and have extensive records of methods development for high-throughput structure determination and analysis. The consortium will have centralized facilities that will carry out an increasing fraction of routine tasks such as protein production, crystallization, and x-ray data collection. P-21 researchers are responsible for overseeing the primary x-ray data-collection facility (beamline X8-C at Brookhaven). In addition, we are developing new methods and instrumentation for improved data collection and analysis.

Functional Brain Imaging

A recent unpublished NIH position paper states “Brain imaging is one of the most rapidly advancing fields in science today.” More than any other area of biology, it is a field in which the progress of research is dependent on improving technologies and computational power.

> *“…[R]apid improvements in brain-imaging methods provide our best hope for understanding brain mechanisms that play a role in mental illness and, eventually, for improving our ability to diagnose, treat, and prevent neurologically based brain disorders.”*

P-21’s effort in functional brain imaging focuses on the combined use of magnetoencephalography (MEG), anatomical MRI, functional MRI (fMRI), and optical-imaging techniques to develop improved techniques for noninvasive imaging of the human brain. High-resolution MEG arrays and optical-imaging techniques are also used to image neural activity directly from the brains of experimental animals (see Figure 2). Together with collaborators at the University of New Mexico School of Medicine, Albuquerque Regional Federal Medical Center in New Mexico, Massachusetts General Hospital in Boston, and the University of Minnesota School of Medicine in Minneapolis, P-21’s work in functional brain imaging contributed significantly to the recent formation of the $60M National Foundation for Functional Brain Imaging to be headquartered in Albuquerque.

Members of P-21 are engaged in projects to design improved multichannel magnetic sensors, develop more accurate mathematical models for localizing the electrical and magnetic signals from the brain, validate MEG using known current sources in computational and physical models of the brain, and use MEG to address important questions in basic neuroscience and in research on neurological and psychiatric disorders.

Combining MEG and anatomical MRI with other functional imaging techniques such as fMRI and positron emission tomography (PET) offers the opportunity of increasing the combined spatial and temporal resolution of functional imaging techniques well beyond that of any single method, as noted in the NIH quotation above. We are engaged in developing mathematical models for combining these alternative forms of brain imaging. This work is part of a nationwide effort to develop three-dimensional (3-D) computational models of the brain in which a variety of structural and functional information can be represented for storage, retrieval, and analysis.

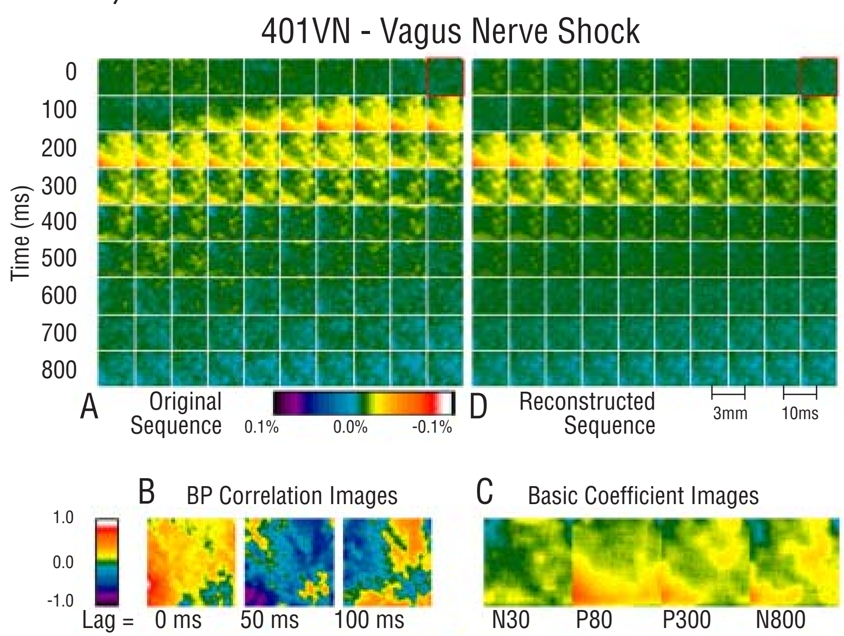


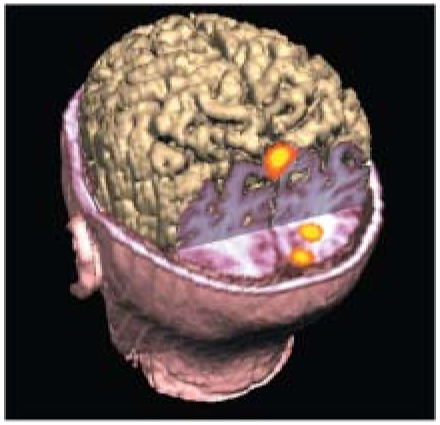
Figure 2. High-resolution optical-imaging techniques allow for images such as this, which accurately measure neural activity directly from the brain.

SQUID-Based Sensors and Applications

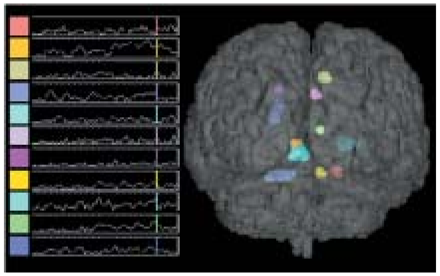
The goals of our MEG SQUID sensor projects are to develop, test, and evaluate sensor systems, numerical techniques, and computational models for functional imaging of the human brain using MEG. MEG involves the use of SQUIDs to measure magnetic fields associated with human brain activity. Measurement of the magnetic fields of the brain (which are approximately a billion times smaller than Earth's) requires sensitive magnetic sensors, magnetic shielding from the environment (currently implemented through a shielded room), and advanced signal-enhancement and modeling techniques. Because magnetic fields readily penetrate the skull, MEG offers the potential for noninvasive measurement of brain function in much the same way that computed tomography and MRI allow the noninvasive detection of brain structure. MEG has therefore generated considerable interest in its possible use as a tool in basic neuroscience for functional mapping of the human brain, as a clinical tool for the assessment of neurological and psychiatric disorders, as a possible source of signals for use in the development of neural prosthetics and human-machine interfaces, and in other applied contexts.

MEG directly measures a physical effect of neuronal currents with temporal resolution not limited by the sluggish vascular response, unlike PET and fMRI that measure hemodynamic changes associated with neuronal activity. High temporal resolution is particularly important for studying neurological disorders such as epilepsy, where temporal information is a major diagnostic, and for fundamental studies of synchronization and oscillatory brain activity. Our whole-head MEG system is based on the P-21 patented principle of superconducting image-surface gradiometry, where magnetic sources are imaged on the surface and magnetometers near the surface sense the combined fields as if the sensors were gradiometers (see Figure 3). Fabrication and assembly of this system are nearly complete. This system will play a major role in the National Foundation for Functional Brain Imaging.

Significant progress has also been made in development of novel, improved approaches to the MEG forward and inverse problems. In the case of the forward problem, the two major existing approaches are spherical (or spherical-shell) models and boundary-element models. Spherical models have the advantage of computational simplicity, but they can result in significant inaccuracies in regions of the head that depart from spherical geometry. In contrast, boundary-element models are more accurate but at a significant increase in computational complexity. Working with our collaborators, we have developed an alternative to the spherical and boundary-element approaches to the forward problem, termed the weighted multisphere approach because it uses multiple spheres fit to the local curvature of the skull.



(a)



(b)

Figure 3. In our whole-head MEG system (shown in Fig. 1), the locations and time courses of active neural populations are calculated using computer models (a) and displayed on MRI images of brain anatomy (b).

This approach can achieve accuracies approaching those of the boundary-element model with computation time comparable to that of the simple spherical model. With respect to the inverse problem, members of P-21 recently demonstrated a new probabilistic approach based on Bayesian inference. Unlike all other approaches to the inverse problem, this approach does not result in a single "best" solution to the problem. Rather, it estimates a probability distribution of solutions upon which all subsequent inferences are based. This distribution provides a means of identifying and estimating the features of current sources from surface measurements that are most probable among the multiple solutions and can account for any set of surface MEG measurements. The promise of this approach has been demonstrated using computer simulations and experimental data. In particular, we have demonstrated for the first time that information can be extracted not only about the locations of regions of activity but also their extent.

In addition to applications of SQUIDs to MEG and related biological applications, members of P-21 have made significant accomplishments in applying these same sensors to the nondestructive evaluation of nuclear weapons components and materials. As described in detail in a research highlight in Chapter 2 of this report "SQUID Array Microscope —An Ultrasensitive Tool for Nondestructive Evaluation," a SQUID microscope has been designed, built, and tested for applications in the Enhanced Surveillance Program. This system uses a SQUID cooled by liquid nitrogen to map magnetic fields produced by eddy currents in a sample at room temperature. Material defects in the sample (due, for example, to cracks, seams, stress fractures, corrosion, or separation of layers) perturb eddy currents and produce magnetic-field anomalies when compared to uniform, defect-free materials. Such anomalies can be detected even if the material defects are located below the surface in deeper layers of the sample. This latter capability is particularly important for nondestructive evaluation of weapons components and materials.

In the first full year of the project, the SQUID microscope team designed, fabricated, and performed successful initial tests of a SQUID microscope based on high-critical-temperature SQUID sensors. This work won P-21's SQUID Microscope Team a Los Alamos Distinguished Performance Award for 1998. Their success was based in part on their ability to exploit P-21's extensive experience in applications of SQUID sensors for noninvasive measurement of human brain function. Given this successful proof of concept, the team is now refining the SQUID microscope design to improve its sensitivity and resolution, to permit operation in magnetically noisy environments, and to use higher-frequency induction fields.

Biologically Inspired Hardware, Computation, and Robotics

P-21 is making a significant effort in the study of adaptive and biologically inspired computation. Biological systems are capable of processing sensory information distributed across tens of thousands of input channels and are furthermore able to do so in real-time. Modern digital computers, however, are typically overwhelmed when confronted with similar massively parallel input streams. Unlike man-made sensors, which encode input signals as simple scalar magnitudes, biological neurons represent information as trains of uniform impulses. By transiently synchronizing their impulse activity, biological networks exploit this extra encoding dimension in order to separate signal from noise and to separate multiple signals in the input space from each other. We are beginning a study to make use of existing expertise, both at the Laboratory and among our university collaborators, to further explore and develop this promising new field of technology. A specific application is autonomous, visually guided navigation. We are approaching this area using modeling of visual neuronal processes and application of hardware neuromorphic chips developed by collaborators at the University of Delaware and by developing and testing algorithms used to autonomously guide a small wheeled vehicle. For more information on this research, see the research highlight "Synchronization of Spiking Neurons in a Computer Model of the Mammalian Retina" in Chapter 2.

Single Molecule Spectroscopy and Electrophoresis

P-21 and its collaborators have extended their work on the detection and characterization of single molecules in a liquid. The goal of this research is to measure and characterize the spectroscopic properties of individual molecules (see Figure 4). Such spectroscopic measurements can be used to identify the presence of a particular molecular species in an extremely dilute solution, or they can be used to probe the local environment that surrounds an individual molecule. The former capability promises a new level of speed and sensitivity for medical diagnostics, whereas the latter capability makes it possible to study properties of biological systems that cannot be measured when a lack of sensitivity confines measurements to the determination of the average properties of a large ensemble of microenvironments. Thus far, the spectroscopic properties measured at the single-molecule level include emission spectra, fluorescence lifetime, and total emission intensity. Recently the single-molecule spectroscopic approach has been extended to include single-molecule electrophoresis and approaches to ultrasensitive detection of viral and bacterial pathogens in soil and water samples. See the research highlight "Single-Molecule Detection of Specific Nucleic-Acid Sequence" in Chapter 2. We are exploring additional applications for basic research and for medical diagnostics.

Figure 4. The single-molecule electrophoretic analyzer detects single labeled molecules in solution.

High-Speed Electronics Team

Already a diverse group, P-21 became more diverse and significantly stronger with the addition in December 1997 of the electronics team formerly in the Hydrodynamics and X-Ray Physics Group (P-22). Previously a key element of the nuclear test program at the Nevada Test Site, the electronics team refocused its efforts to other defense and civilian needs with the cessation of nuclear testing. We now, quite literally, have the capability within P-21 to take an idea from the "gleam-in-the-eye" stage, through basic and applied research, to a fully developed, fieldable instrument for direct use by sponsors or industrial partners. The electronics team brings substantial capabilities in electronics design, fabrication, and implementation to P-21 that are of great value in their own right and have significant potential for the enhancement of our biological programs. In less than one year, the electronics team has made contributions in all of the focus areas listed above, including exploration of detectors derived from remote ultra-low light imaging (RULLI) techniques for applications in biomedical imaging and single molecule detection, contributions to high-throughput protein purification for the structural genome project, and other areas.

Currently the major effort of the high-speed electronics team is development and application of ultra low-light imaging through the RULLI project. They have demonstrated the capability to build remote images from a variety of platforms using only the ambient illumination provided by starlight. The team has also demonstrated active imaging of objects using a laser illuminator and precise timing to produce a three-dimensional literal image cube. The team is working to both improve and extend the technology as well as to apply it to various problems including imaging of optical signals rising from nerve activity, understanding the propagation of light in clouds, and national-security applications.

Further Information

For further information on P-21's projects, refer to the project descriptions in Appendix A of this progress report. Some of our major achievements are also covered as research highlights in Chapter 2, as mentioned above. These include SQUID microscope development, single-molecule detection, neuronal synchronization research, and the development of the virtual pinhole confocal microscope.

References

[1] D. A. Doyle, J. M. Cabral, R. A. Pfuetzner, *et al.*, "The Structure of the Potassium Channel: Molecular Basis of K^+ Conduction and Selectivity," *Science* 280, 69 (1998).